

# USE OF NEUTRON ACTIVATION ANALYSIS FOR STUDYING STABLE IODIDE UPTAKE BY THE THYROID \*

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Measurement of the rate of accumulation of radioiodine by the thyroid gland is of considerable clinical value, since in most instances an avid uptake of radioiodine may be correctly assumed to be due to a high rate of uptake of stable iodide by the thyroid. This measurement, expressed as a percentage of the administered radioiodine dose accumulated per unit time by the thyroid, does not give a quantitative measurement of the stable inorganic iodide being accumulated by the gland. Occasionally an avidity for radioiodine may be attributable to an abnormally small extrathyroidal iodide pool, as in the case of the patients with endemic goiter described in the classic report of Stanbury and his associates (1).

In 1949 Stanley described a method for the measurement of stable iodide accumulation by the thyroid gland using the radioiodine uptake of the thyroid and the specific activity of simultaneously excreted urine; i.e., the ratio of radioactive to stable iodide in the urine (2). The technique extended the information obtainable by the study of radioiodine accumulation alone. Technical difficulties associated with the chemical measurement of trace quantities of stable inorganic iodide have prevented its widespread application to studies of thyroid disease. The purpose of this paper is 1) to describe a new technique for the accurate and sensitive measurement of iodide in biological fluids, and 2) to present the results of its use in studies of the relationship between plasma inorganic iodide concentration and iodide accumulation by the human thyroid gland.

## METHODS

*Principles of activation analysis.* Since its introduction by Hevesy in 1935, neutron activation analysis has been

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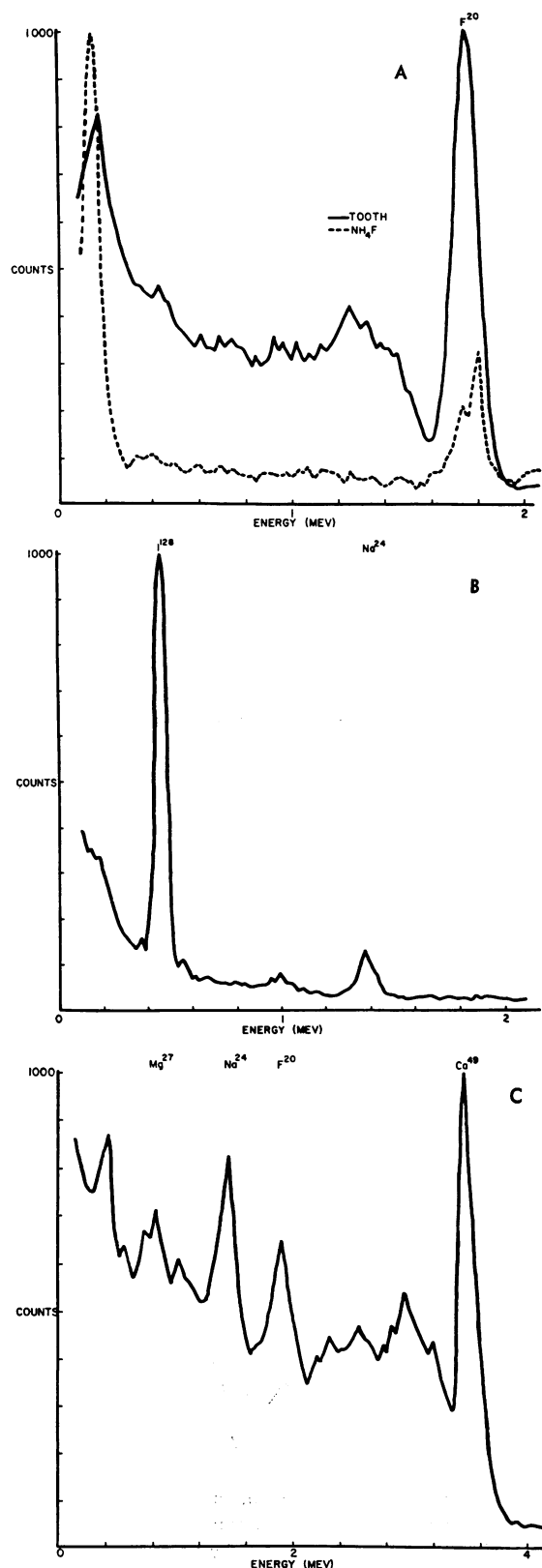
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developed into one of the most sensitive and accurate methods for the determination of trace elements. The element to be determined is made radioactive by neutron irradiation, usually carried out in a nuclear reactor, and is identified by the characteristic gamma-ray emission and rate of decay of the resulting radionuclide. Quantitative measurements are possible, since the amount of radioactivity induced is proportional to the amount of the element present.

In some tissues trace elements are sufficiently concentrated to be measured without chemical separation prior to activation. For example, gamma-ray spectra of the radioactivity induced in human tooth, thyroid, and bone are shown in Figure 1. The gamma spectrum of tooth after 1 minute's activation was very similar to the spectrum obtained from activation of ammonium fluoride. The photopeak energy (Figure 1A) and the half-life were characteristic of fluorine<sup>20</sup>. The gamma spectrum of human thyroid tissue included the characteristic photopeak of iodine<sup>128</sup> and had an identical half-life (Figure 1B). Figure 1C shows the result of 10-minute activation of normal human bone. The gamma spectrum had the photopeaks of calcium<sup>40</sup>, fluorine<sup>20</sup>, sodium<sup>24</sup>, and magnesium<sup>27</sup>.

In most biological materials it was not possible to detect trace elements by neutron activation without removing the large quantities of sodium and chlorine that dominated the gamma-ray spectrum. Spencer, Mitchell and King (3) presented the results of neutron irradiation of serum. Gamma emissions from Na<sup>24</sup> and Cl<sup>38</sup> prevented application of the technique to studies of trace elements in serum. Similarly, activation of normal urine for 1 hour produced a gamma-ray spectrum identical with that of sodium chloride (Figure 2). Utilization of differential activation times or differential decay times to measure iodide in the presence of large amounts of chloride was impossible because of the similar half-lives of chlorine<sup>38</sup> (37 minutes) and iodine<sup>128</sup> (25 minutes); to measure iodide (or bromide) in urine, it was necessary to separate these halogens from chloride and sodium prior to activation.

*Analytical procedure for measurement of urinary iodide.* Urine samples that had been collected in iodine-free containers were passed at a flow rate of approximately 100 ml per hour through polyethylene columns (5 cm long, 0.6 cm diameter) containing 0.8 ml of Amberlite IRA-400 anionic exchange resin (Cl<sup>-</sup> form). Urinary iodide was adsorbed by the column, while sodium and other cat-



ions passed through. The chloride on the resin column was then preferentially eluted with 60 ml of 0.013 M ammonium thiocyanate solution. At this volume and concentration, thiocyanate was able to displace chloride without displacing iodide from the resin. With iodine<sup>131</sup> or iodine<sup>132</sup> as tracer, the recovery of iodide from this procedure was determined for each sample studied. The resin columns were then wrapped in plastic film to prevent contamination. After the radioiodine had decayed sufficiently,<sup>1</sup> the resin columns were activated for 1 hour in the National Naval Medical Center reactor at a thermal neutron flux of  $2.25 \times 10^8$  neutrons per cm<sup>2</sup> per second.

After activation the samples were placed in a scintillation detector, a 2.75-inch diameter well-shaped sodium iodide crystal. Gamma-ray spectra were determined on a 100-channel pulse height analyzer. A typical spectrum of a urine sample after activation is shown in Figure 3. The photopeaks are those of iodine<sup>128</sup>, bromine<sup>80</sup> and residual chlorine<sup>38</sup>. The resin blank and the polyethylene container showed negligible induced radioactivity at this neutron flux. It can be seen (Figure 3) that the Compton radiation from the residual chlorine<sup>38</sup> and bromine<sup>80</sup> contributed to the radioactivity measured at the iodine<sup>128</sup> photopeak. Therefore it was necessary to subtract this activity to obtain the true count rate of iodine<sup>128</sup>. With each unknown sample, the amount of iodide on the resin column was calculated by comparing its induced activity with the activity induced in iodide standards of known weight activated on identical resin columns under identical conditions. The relationship between induced iodine<sup>128</sup> radioactivity and the iodide content of standard solutions of ammonium iodide in a typical experiment is shown in Figure 4. There was a linear response of 37 cpm per  $\mu\text{g}$  iodide. This induced radioactivity was very reproducible ( $\pm 5$  per cent) and agreed with the radioactivity predictable for the neutron flux and the detection system employed.

*Experimental procedure used to measure iodide uptake by the thyroid.* The procedure used in patients to measure the urinary excretion and thyroid uptake of stable iodide was as follows. The studies were begun at 9 a.m. with the patients in the fasting state. After the patient had emptied his bladder, a tracer dose of 4  $\mu\text{C}$  of carrier-free sodium iodide<sup>131</sup> or 10  $\mu\text{C}$  of carrier-free sodium iodide<sup>132</sup> was given. Both the oral and intravenous routes of administration were studied. At the end of 2 hours thyroid uptake was measured with a flat-field collimated 2.75-inch sodium iodide scintillation detector, gamma-ray

<sup>1</sup> I<sup>132</sup> was more suitable than I<sup>131</sup>, since the shorter half-life of 2.3 hours permitted activation 24 hours after collection of the urine.

FIG. 1. **A.** GAMMA-RAY SPECTRUM OF HUMAN TOOTH COMPARED WITH THAT OF AMMONIUM FLUORIDE. **B.** GAMMA-RAY SPECTRUM OF HUMAN THYROID; I<sup>128</sup> IS THE PRINCIPAL PHOTOPEAK OF THE SPECTRUM. **C.** GAMMA-RAY SPECTRUM OF HUMAN BONE; PHOTOPEAKS ARE Ca<sup>40</sup>, F<sup>20</sup>, Na<sup>24</sup>, AND Mg<sup>77</sup>.

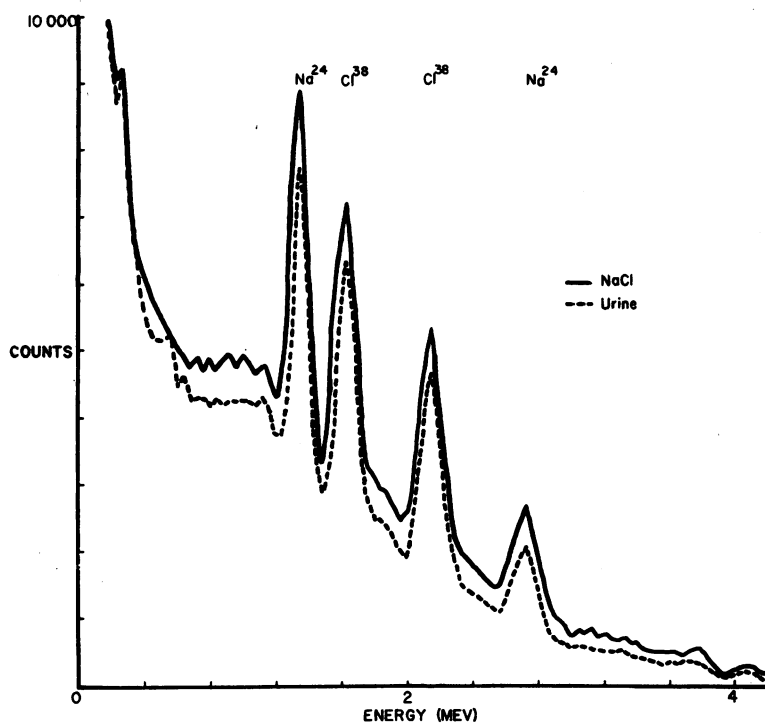


FIG. 2. GAMMA-RAY SPECTRUM OF URINE IS SIMILAR TO THAT OF SODIUM CHLORIDE.

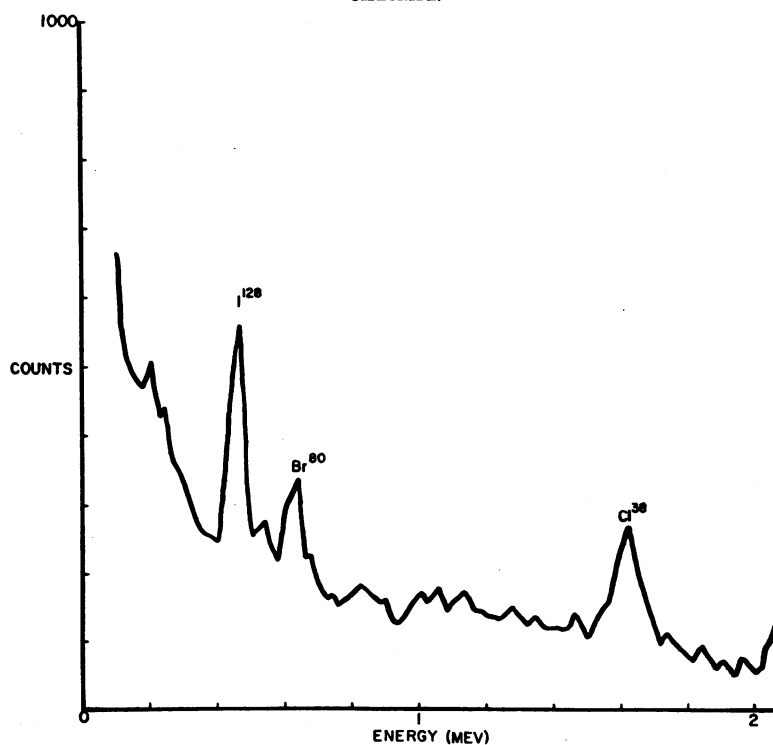


FIG. 3. GAMMA-RAY SPECTRUM OF A RESIN COLUMN AFTER ADSORPTION OF URINE AND ELUTION WITH 60 ML OF 0.013 M AMMONIUM THIOCYANATE. The photopeaks are iodine<sup>128</sup>, bromine<sup>80</sup>, the residual chlorine<sup>38</sup> not eluted by the thiocyanate.

spectrometer, and ORINS standard thyroid uptake phantom. The thyroid uptake was expressed as

$$\frac{\text{neck radioactivity} - \text{radioactivity with thyroid shielded}}{\text{dose radioactivity in standard phantom} - \text{radioactivity with dose in phantom shielded}} \times 100$$

In  $I^{131}$  studies, a 1.5 cm-thick lead shield was used to eliminate the thyroidal radioactivity; a 5 cm-thick shield was used in  $I^{132}$  studies because of the increased gamma energy from the latter nuclide.

A further correction for extrathyroidal radioactivity was determined by studies in which 10 euthyroid subjects were given large doses of Lugol's solution to completely block thyroid uptake. Neck measurements were made 2 hours after the intravenous injection of  $I^{131}$  and  $I^{132}$  (five subjects for each isotope). The radioactivity counted beneath the lead shield was  $2.6 \pm 0.4$  per cent dose (mean  $\pm 1$  SD) for  $I^{132}$  and  $2.5 \pm 0.8$  per cent dose for  $I^{131}$ . These values were subtracted from the thyroid uptake measurements in calculation of the uptake rates of stable iodide.

Immediately after the thyroid measurement the patient urinated into a disposable iodine-free container. The collected urine was then passed through one of the previously described resin columns. Recovery of iodide by the resin column was measured, with the  $I^{131}$  or  $I^{132}$  as a tracer. The percentage of the administered dose of radioiodine on the resin column was measured by comparing it with a standard containing one-tenth of the dose adsorbed by a blank resin column and counted under identical geometric conditions.

After the administered radioiodine had decayed to negligible levels, the stable iodide content of each resin

column was measured as described previously. The thyroid uptake of stable iodide was calculated according to the following formula:

$$\text{thyroid uptake (TU) } (\mu\text{g}/2 \text{ hrs}) = \frac{\text{TU } (\% \text{ dose } I^{131}/2 \text{ hrs}) \times \text{urine iodide excretion } (\mu\text{g}/2 \text{ hrs})}{\text{urine excretion } (\% \text{ dose } I^{131}/2 \text{ hrs})}$$

In five subjects selected as euthyroid, the relationship between plasma inorganic iodide concentration and thyroid iodide accumulation was measured at various plasma inorganic iodide levels produced by exogenous iodide administration. These subjects were hospitalized on the research ward of the Johns Hopkins Hospital, and received a usual hospital diet. After control studies iodine was given orally every 4 hours as potassium iodide. The daily dose was increased progressively over a 2-week period from 1,200 to 7,200  $\mu\text{g}$  per day. In three subjects iodide administration at a level of 10,000  $\mu\text{g}$  per day was continued for an average of 37 days. Radioiodine accumulation was measured daily for 12 days; thereafter it was measured weekly. Radioiodine ( $I^{132}$ ) was given intravenously 2 hours after the 8 a.m. oral iodide dose. Measurement of stable and radioactive urinary iodide was performed as previously described.

Plasma iodide concentration 1 hour after administration of the dose was measured by comparing the radioactivity of the plasma with a standard containing 1/25 of the dose. The sample was obtained at the midpoint of the urine collection period. The plasma iodide concentration was calculated, using the urinary specific activity as follows:

$$\frac{\% \text{ dose } I^{132}/5 \text{ ml plasma}}{\mu\text{g } I^{127}/5 \text{ ml plasma}} = \frac{\% \text{ dose } I^{132} \text{ urine}}{\mu\text{g } I^{127} \text{ urine}}$$

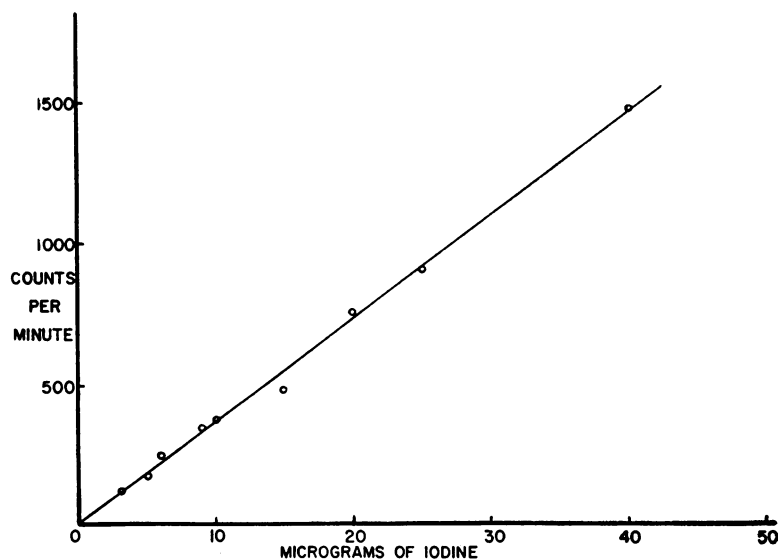


FIG. 4. RELATIONSHIP BETWEEN IODIDE CONTENT ( $\text{NH}_4\text{I}$  STANDARDS) AND INDUCED RADIOACTIVITY AS MEASURED IN THE PRESENT SYSTEM.

or

$$\frac{\mu\text{g } I^{127}}{5 \text{ ml plasma}}$$

$$= \frac{\mu\text{g } I^{127} \text{ urine} \times \% \text{ dose } I^{132}/5 \text{ ml plasma}}{\% \text{ dose } I^{132} \text{ urine}}$$

## RESULTS

*I. Study of euthyroid subjects.* Thirty-four euthyroid subjects were studied (Table I). The mean uptake of stable iodide corrected for total neck extrathyroidal radioactivity was  $5.9 \pm 4.4$  (mean  $\pm$  SD)  $\mu\text{g}$  per 2 hours (range, 1 to 20  $\mu\text{g}$  per 2 hrs). The mean excretion of stable iodide

was  $16.9 \pm 9.4$   $\mu\text{g}$  per 2 hours (mean  $\pm$  SD). The radioiodine uptake ranged from 4 to 13 per cent per 2 hours. In 15 euthyroid subjects the plasma concentration of stable iodide was determined 1 hour after administration of the tracer dose. The mean value was 5  $\mu\text{g}$  per L (range, 1 to 10  $\mu\text{g}$  per L).

Of particular interest was the finding that the subjects with the highest excretion of stable iodide did *not* have a radioiodine uptake significantly different from those with lower urinary iodide excretion rates. In addition, over the range of plasma iodide concentration observed in these

TABLE I  
Stable and radioiodine measurements in euthyroid subjects

Subj.	Urine excret.	Urine excret.	Urine spec. activ.	Thyroid uptake*	Thyroid uptake†	Thyroid uptake	Extrathy. iodide pool‡	Extrathy. iodide pool	Plasma inorg. iodide
no.	% dose/2 hrs	$\mu\text{g } I^{127}/2 \text{ hrs}$	$\mu\text{g } I^{127}/1\% \text{ dose radioiodine}$	% dose/2 hrs	% dose/2 hrs	$\mu\text{g } I^{127}/2 \text{ hrs}$	% dose	$\mu\text{g } I^{127}$	$\mu\text{g } I^{127}/\text{L}$
1	28.4	22.3	0.78	6.0	3.5	2.4	83.0	64.7	
2	14.2	8.0	0.56	8.0	5.5	4.5	92.0	51.5	
3	13.2	8.8	0.67	4.3	1.8	3.7	91.5	61.3	
4	15.4	10.8	0.70	6.0	3.5	2.4	89.5	62.6	
5	20.8	9.2	0.44	5.7	3.2	1.4	88.0	38.8	
6	20.2	16.6	0.81	5.2	2.7	2.2	88.5	71.6	
7	9.6	18.7	1.95	9.0	6.5	12.7	92.0	179.2	
8	8.4	16.3	1.94	4.3	1.8	3.5	94.9	184.0	
9	13.0	35.4	2.71	9.7	7.2	19.5	88.9	241.9	
10	17.1	30.0	1.75	6.5	4.0	7.0	89.4	156.5	
11	24.3	17.3	0.72	5.2	2.7	1.9	86.5	62.3	
12	22.8	20.6	0.91	9.2	6.7	6.0	85.2	76.6	
13	13.3	26.8	2.02	6.8	4.3	8.7	91.2	184.0	
14	29.8	31.9	1.07	4.1	1.6	1.7	84.2	90.0	
15	23.1	8.2	0.35	8.6	6.1	2.1	85.4	29.8	
16	18.0	28.2	1.57	6.6	4.1	6.4	89.0	139.5	
17	12.2	29.2	2.40	5.9	3.4	8.2	91.2	218.2	
18	6.8	2.0	0.29	7.9	5.4	1.6	93.9	27.2	2.0
19	22.9	16.8	0.73	9.6	7.1	5.2	85.0	62.3	
20	9.4	10.3	1.10	7.5	5.0	5.5	92.8	102.0	
21			1.86	10.7	8.2	15.2			10.0
22	14.2	14.2	1.00	8.1	5.6	5.6	90.1	90.1	5.0
23	22.6	6.0	0.26	7.8	5.3	1.5	86.0	22.7	1.0
24	7.8	4.5	0.57	13.0	10.5	6.0	91.8	52.2	6.0
25	5.0	7.1	1.42	5.9	3.4	4.7	95.8	137.5	7.0
26	10.9	20.7	1.90	9.6	7.1	7.3	91.0	93.9	9.0
27	13.8	9.8	0.71	9.0	6.5	4.6	88.8	63.0	4.0
28	12.3	12.7	1.03	6.0	3.5	3.6	92.1	95.0	8.0
29	21.0	23.3	1.11	6.3	3.8	4.2	87.6	97.1	8.0
30	21.7	23.0	1.06	11.5	9.0	9.4	84.6	89.7	7.0
31	16.0	6.5	0.41	11.0	8.5	3.5	87.7	35.8	2.0
32	17.3	9.9	0.57	8.9	6.4	3.6	88.1	50.3	4.0
33	16.0	16.9	1.02	10.4	7.9	8.1	88.1	90.0	4.0
34	22.2	36.2	1.63	12.4	9.9	16.2	84.0	136.5	5.0
Mean	16.5	16.9		7.8	5.4	5.9		95.7	5.0
SD	6.3	9.4		2.4	2.3	4.4		56.8	3.0

\* Corrected by neck minus shielded-neck method.

† Additional correction by thyroid block for total neck extrathyroidal radioactivity.

‡ Calculated as follows:

$$100\% \text{ dose radioiodine} - \left[ \frac{1}{2} \text{ thyroid uptake } (\% \text{ dose}/2 \text{ hrs}) + \frac{1}{2} \text{ urine excretion } (\% \text{ dose}/2 \text{ hrs}) \right].$$

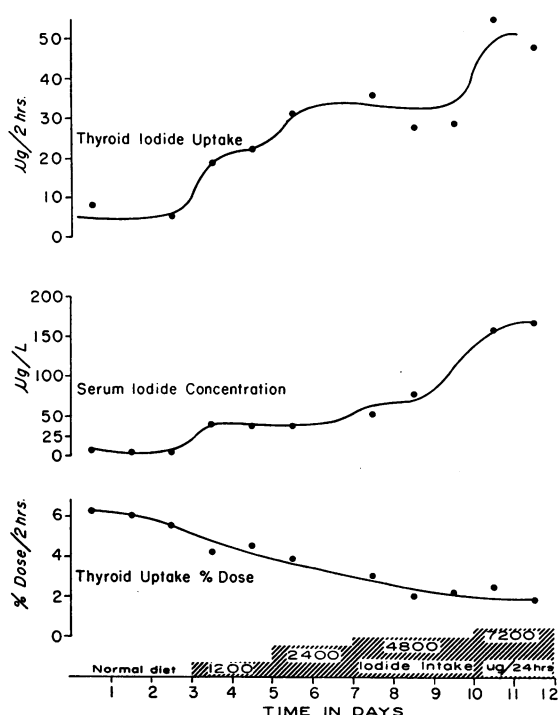


FIG. 5. MEASUREMENTS OF ACCUMULATION OF  $I^{131}$  AND  $I^{132}$  BY THE THYROID DURING THE FIRST 10 DAYS OF INCREASED IODIDE INTAKE IN A EUTHYROID SUBJECT. Plasma inorganic iodide concentration is shown.

subjects, stable iodide uptake by the thyroid was highest in those subjects with the highest concentration of inorganic iodide in their plasma. As a result of these findings, the study was extended as described in the following section.

*II. Relationship between serum iodide level and the accumulation of iodide by euthyroid subjects.* Selected euthyroid subjects were hospitalized and received a usual hospital diet. After control studies iodine was given orally every 4 hours as potassium iodide. The daily dose was increased progressively over a 2-week period from 1,200 to 7,200  $\mu\text{g}$  per day. In three subjects iodide administration at a level of 10,000  $\mu\text{g}$  per day was continued for an average of 37 days. Stable and radioiodine accumulation was measured daily for 12 days; thereafter it was measured weekly.

An example of the first 12 days of a typical study is presented in Figure 5. During the control period, when no exogenous iodide was added to the diet, the patient's 2-hour thyroid uptake (per cent dose) was 6 per cent on successive days. The patient excreted 15 and 14  $\mu\text{g}$  of inorganic

iodide per 2 hours. The thyroid uptake of stable iodide was 8 and 5.5  $\mu\text{g}$  per 2 hours. Corresponding plasma concentrations were 7 and 5  $\mu\text{g}$  per L. During administration of potassium iodide, begun on the fourth day, the uptake of radioiodine ( $I^{132}$ ) by the thyroid gradually decreased. By Day 12 it had decreased to 1.9 per cent dose per 2 hours. Concurrently, the urinary excretion of  $I^{127}$  increased progressively to 418  $\mu\text{g}$  per 2 hours. In contrast to the decreasing radioiodine uptake, the uptake of stable iodide increased from 7  $\mu\text{g}$  per 2 hours during the control period to 42  $\mu\text{g}$  per 2 hours on Day 12. The plasma inorganic iodide concentration increased to 169  $\mu\text{g}$  per L.

Thus it was found that, as the iodide intake increased from 1,200 to 7,200  $\mu\text{g}$  per day, the thyroid uptake of radioiodine decreased. However, the concomitant increase in plasma iodide concentration resulted in a progressive accumulation of stable iodide despite the decreased radioiodine accumulation.

Each of the five euthyroid subjects studied during iodide administration showed a similar pattern during the first 2 weeks. A summary of the results in the five patients is presented in Figure 6. At each level of iodide intake, extending over the entire period of 37 days, the thyroid uptake is shown both as a percentage of the radioiodine dose and as uptake of stable iodide. Despite the fall in radioiodine accumulation as the iodide intake increased, iodide accumulation increased rapidly until the intake reached 5,500  $\mu\text{g}$  per day. Thereafter it fell steadily, but even after more than a month of high iodide intake, stable iodide accumulation exceeded control levels. In one subject the uptake of stable iodide was 75  $\mu\text{g}$  per 2 hours while receiving 7,200  $\mu\text{g}$  iodide per day.

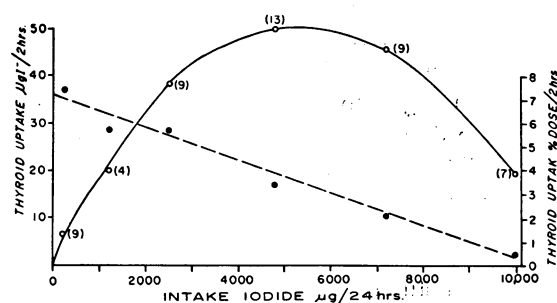


FIG. 6. RELATIONSHIP BETWEEN IODIDE ADMINISTRATION AND THYROID UPTAKE OF STABLE IODIDE DURING THE 37-DAY PERIOD OF IODIDE ADMINISTRATION.

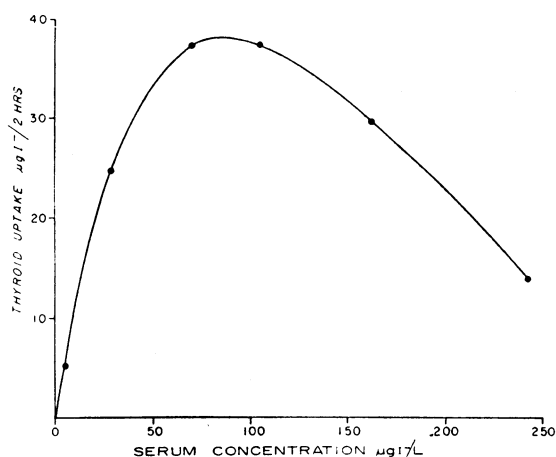


FIG. 7. RELATIONSHIP BETWEEN PLASMA INORGANIC IODIDE CONCENTRATION AND UPTAKE OF STABLE IODIDE BY THE THYROID. The study covered a period of 37 days.

On Day 16 of the study, while on this dose of iodide, the subject was given 20  $\mu\text{C}$  of  $\text{I}^{131}$ . The 2-hour radioiodine uptake (corrected for neck extrathyroidal radioactivity) was 3 per cent; 48 hours later 10 per cent of the administered dose remained in the gland. This indicates that the inorganic iodide continued to accumulate during the 2-day period and that iodide initially trapped was not being readily discharged from the gland. This does not imply that synthesis of the trapped iodide was progressing to thyroid hormone, but that the trapped iodide was not merely entering the thyroid and shortly thereafter re-entering the circulation.

The plasma concentration of stable iodide was determined at each level of iodide administration in all five subjects. A total of 51 determinations was made. Figure 7 illustrates that the initial increase in concentration of plasma iodide produced a corresponding increase in the rate of uptake of stable iodide by the thyroid. After the plasma iodide concentration reached 100  $\mu\text{g}$  per L, iodide accumulation began to fall. However, even at the end of the 37-day period of the study, uptake of stable iodide by the thyroid still greatly exceeded control values.

#### DISCUSSION

The present studies were designed to enable measurement of the rate of uptake of stable iodide by the thyroid in micrograms per unit time. A technique of neutron activation analysis was developed

to enable accurate and sensitive measurement of the trace element, iodide, in biological fluids. In the past, application of neutron irradiation techniques to the analysis of trace elements in biological material has been limited by the large quantities of sodium and chloride that dominate the gamma-ray spectrum. The present technique utilized anion exchange resins and selective elution to remove these substances prior to activation.

At the neutron flux employed ( $2.25 \times 10^8$  n/cm<sup>2</sup>/sec) although it was not possible to measure the exceedingly small amounts of inorganic iodide normally present in plasma, urinary iodide concentration could be readily measured. Our basic assumption in measuring the stable iodide uptake by the thyroid was identical with that of Stanley (2), who measured both the radioiodine uptake of the thyroid gland and stable iodide concentration of the simultaneously excreted urine. At any moment after the administration of a tracer dose of radioiodine, the specific activity ( $\text{I}^{131}/\text{I}^{127}$ ) of urinary iodide is the same as that of plasma. This assumption appears justified, since there is no evidence of a renal iodide pool (4). Furthermore, during an experiment in which exogenous iodide was given and plasma iodide was raised to measurable levels, the simultaneous specific activities of serum and urine were nearly identical.

In 34 fasting euthyroid subjects, the mean iodide uptake was  $6 \pm 4$   $\mu\text{g}$  per 2 hours (mean  $\pm$  SD). These values were lower than those of Stanley (2) who found that mean thyroid uptake of iodide in 14 subjects was 10  $\mu\text{g}$  per hour (range, 3 to 19), and of Fitting (5) who found that mean uptake of eight fasting euthyroid subjects was 4.5  $\mu\text{g}$  per hour (range, 1 to 17). More recently, Koutras and co-workers (6) reported the mean iodide uptake of eight euthyroid patients to be  $2.9 \pm 1.3$   $\mu\text{g}$  per hour (mean  $\pm$  1 SD). In the euthyroid subjects of the present study the radioiodine uptake did not correlate with urinary iodide excretion or the plasma concentration of inorganic iodide. Thus, in these subjects, living in an area where there was no iodine deficiency, the radioiodine accumulation by the thyroid did not appear measurably influenced by the day-to-day fluctuations in iodide pool size. Similar results were reported in the normal subjects without evidence of iodide deficiency studied by Koutras and

associates. The correlation between radioiodine accumulation and stable iodide concentration in patients with nontoxic goiter was observed only when the serum iodide concentration was below 1 to 2  $\mu\text{g}$  per L.

Childs and collaborators reported in 1950 that in hyperthyroid subjects, the iodide-trapping function as measured by radioiodine accumulation was not altered with carrier iodide doses in the range 0.1 to 100 mg, but was suppressed by doses of 500 mg or more (7). In contrast, the synthesis of thyroid hormone by the gland was suppressed at lower concentrations (5  $\mu\text{g}$  of inorganic iodide per 100 ml plasma) than those required to suppress the iodide-trapping function. This work extended to hyperthyroid patients the studies of Wolff and Chaikoff who had found that organic binding of iodide by the rat thyroid was blocked so long as plasma iodine remained above 20 to 35  $\mu\text{g}$  per 100 ml (8). However, despite the block in organic binding of iodide, the rat thyroid continued to concentrate iodide.

To study experimentally the effect of large increases in iodide pool size on both radioiodine uptake and the accumulation of stable iodide by the thyroid, five euthyroid subjects were given progressively increasing amounts of oral iodide. As shown in Figure 7, radioiodine uptake decreased as iodide intake increased, but the rate of decrease of radioiodine uptake was very gradual. Consequently, the thyroid accumulated increasing quantities of stable iodide. When iodide intake exceeded 6,000  $\mu\text{g}$  per day, the radioiodine accumulation had decreased to the point that the amount of *stable* iodide accumulated began to decrease despite increasing iodide intake. At the end of 37 days, however, *stable* iodide accumulation by the thyroid still exceeded control levels.

To explain our observations, we suggest the following hypothesis. The thyroid gland accumulates a constant fraction of the extrathyroidal iodide pool; i.e., iodide accumulation approximates a first-order reaction. Thus, day-to-day variations in iodide intake result in corresponding variations in the *amount* of stable iodide accumulated by the thyroid. If we postulate that the iodide concentration gradient in the thyroid gland is maintained by the presence of a carrier with which iodide reacts, how can the first-order dynamics be explained? We must postulate that the

concentration of the carrier is high relative to the iodide concentration in plasma. It is not significantly reduced by its reaction with plasma iodide; consequently, it can be treated as a constant.

Variation in the rate of the first-order reaction—i.e., in the rate of accumulation of radioiodine—is produced by physiological increases or decreases in the concentration of the carrier. For example, prolonged administration of iodide results in a gradual decrease in radioiodine accumulation, presumably until stable iodide accumulation is reduced to normal amounts. This can be seen in the present experiments and is consistent with the clinical observation that prolonged iodide administration does not result in hyperthyroidism. On the other hand, the classic studies of Stanbury and, more recently, of Koutras and co-workers, are consistent with the hypothesis that prolonged iodide deficiency eventually results in an increased amount of carrier substance. This results in an increased rate of the first-order reaction describing iodide accumulation. Consequently, many iodide-deficient patients accumulate normal amounts of iodide and remain euthyroid. That these patients also accumulate iodide by a reaction with first-order dynamics is suggested by the observation of Stanbury that the administration of 1,500  $\mu\text{g}$  of stable iodide daily for as long as a week failed to change the radioiodine uptake.

#### SUMMARY AND CONCLUSIONS

1. In the present study a technique of neutron activation analysis was used to measure trace quantities of inorganic iodide in urine. Anion exchange resins and selective elution permitted removal of interfering sodium and chloride from urine prior to the activation procedure.
2. The uptake of stable iodide by the thyroid was determined by measuring the radioiodine uptake and specific activity ( $I^{131}/I^{127}$ ) of simultaneously excreted urine.
3. In 34 fasting euthyroid subjects the mean iodide uptake by the thyroid was  $3 \pm 2$   $\mu\text{g}$  per hour. Plasma concentration of inorganic iodide averaged 0.005  $\mu\text{g}$  per ml.
4. Day-to-day variations in iodide intake resulted in corresponding variations in the *amount* of stable iodide accumulated by the thyroid, since iodide accumulation approximated a first-order reaction.



5. Prolonged administration of exogenous iodide resulted in a gradual decrease in radioiodine accumulation. This resulted in a decreased accumulation of *stable* iodide only after several weeks of greatly increased iodide uptake by the thyroid.

6. A mechanism postulated to explain the dynamics of iodide accumulation by the thyroid was presented.

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